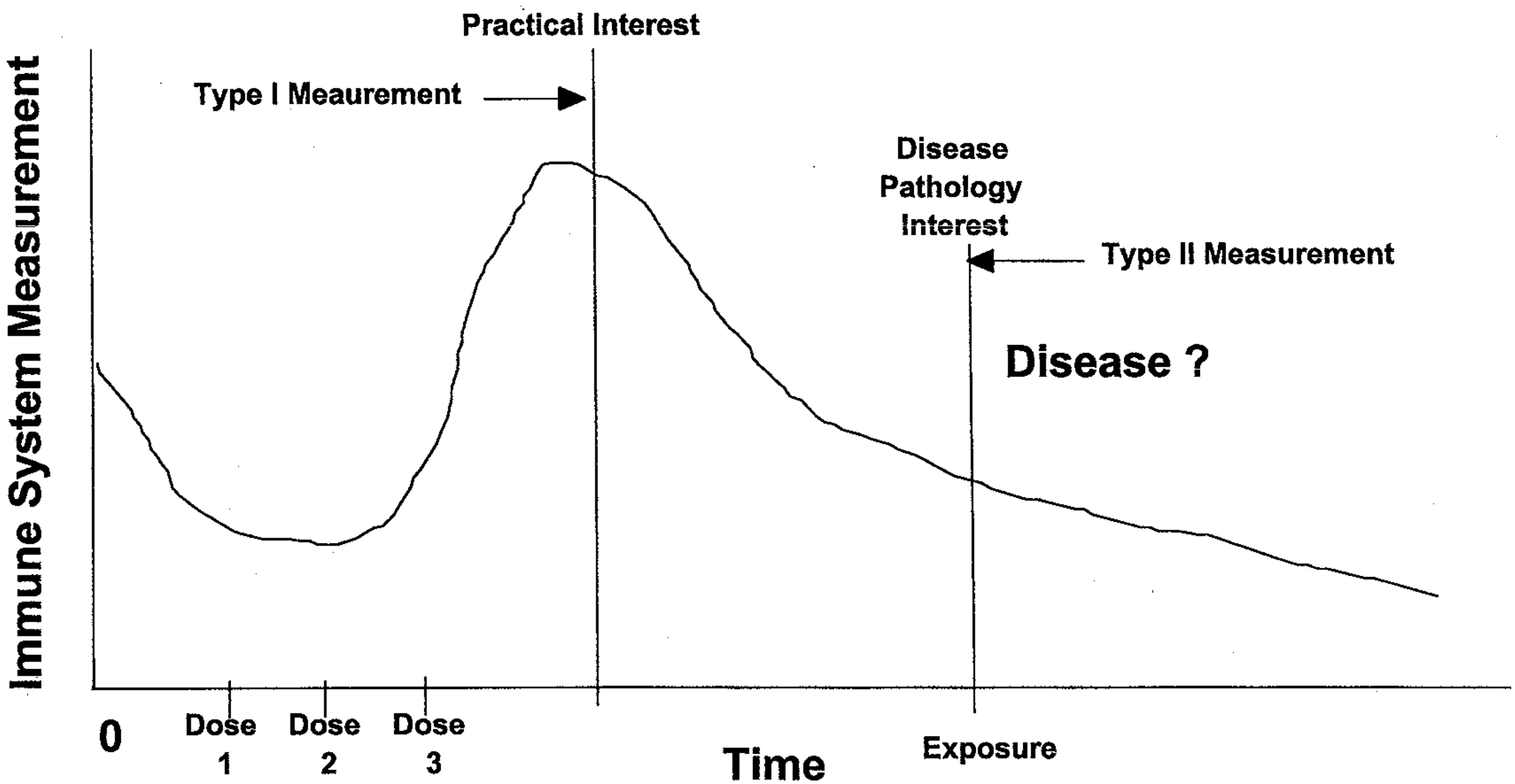
Vaccine Correlates of Immunity

Robert C. Kohberger, Ph.D.
Wyeth-Lederle Vaccines and Pediatrics

Typical Vaccine Trial



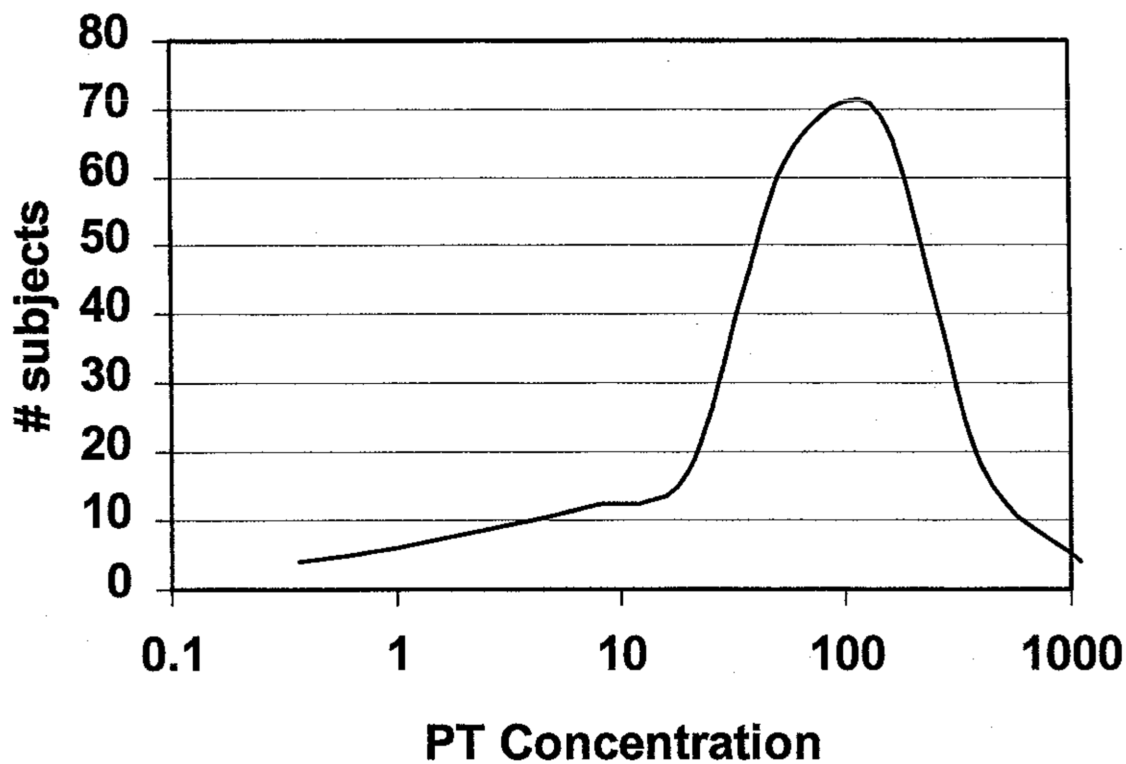
Immune System Measurements

- Humoral immunity
  - based on antibodies which are products of the B cell system
  - antibodies found in body fluids (plasma, lymph, and others)
  - circulating antibody: concentrations measured in plasma
- Cell mediated immunity
  - product of the T cell system

Vaccine Immunogenicity Trials

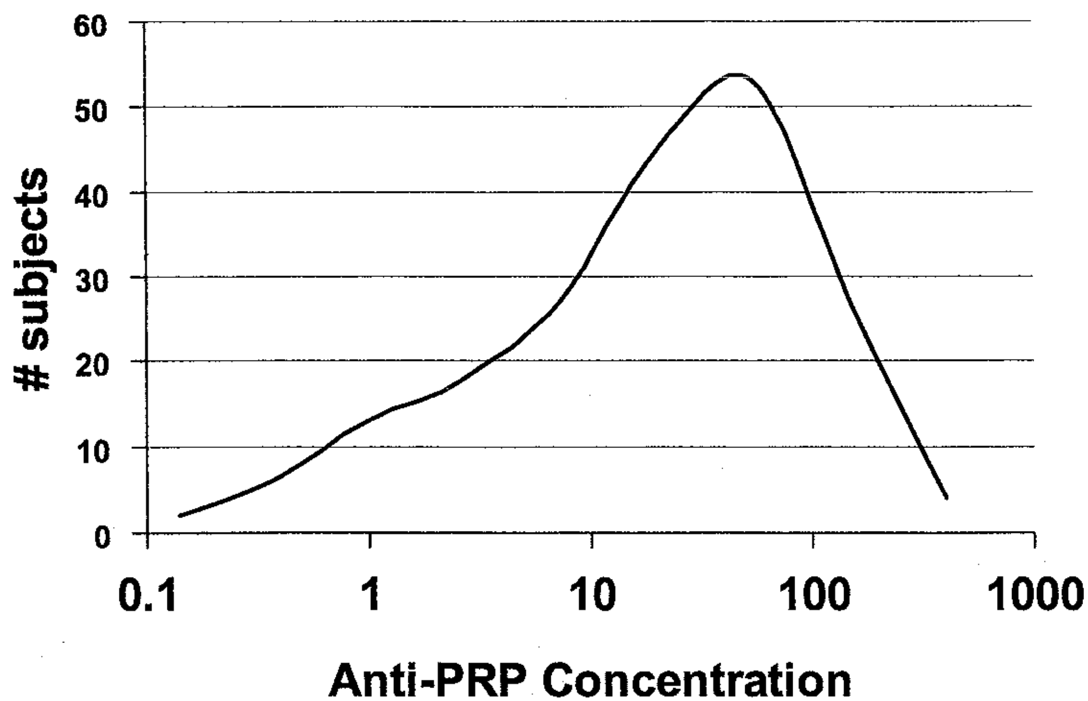
- Antibody concentrations measured shortly after completion of the primary dose series (Type I measurement)
- Antibody concentrations measured immediately prior to infection (Type II measurement)
- Antibody concentrations measured at various times after the completion of the primary series (kinetic studies)

Type I Example: Pertussis Toxin (PT)
GMT = 101.8, std dev = 1.6



Type I Example: Hib (anti-PRP)

GMT = 30.9, std dev = 1.67



Vaccine Efficacy Trials

- Vaccines are intended to prevent the clinical manifestation of diseases
- Efficacy is determined by identifying cases of disease after vaccination and comparing to cases in a placebo group
- Vaccine efficacy is expressed as a reduction in the relative risk of disease

Correlates of Immunity (Protection) Uses

- 'Surrogate' for efficacy
  - allow use of immunogenicity trials (Type I measurements) rather than efficacy trials
- Allow for comparison between different manufacturing processes including combination vaccines
- Allow for prediction of how different antibody response distributions change efficacy

Correlates of Immunity Common Approaches

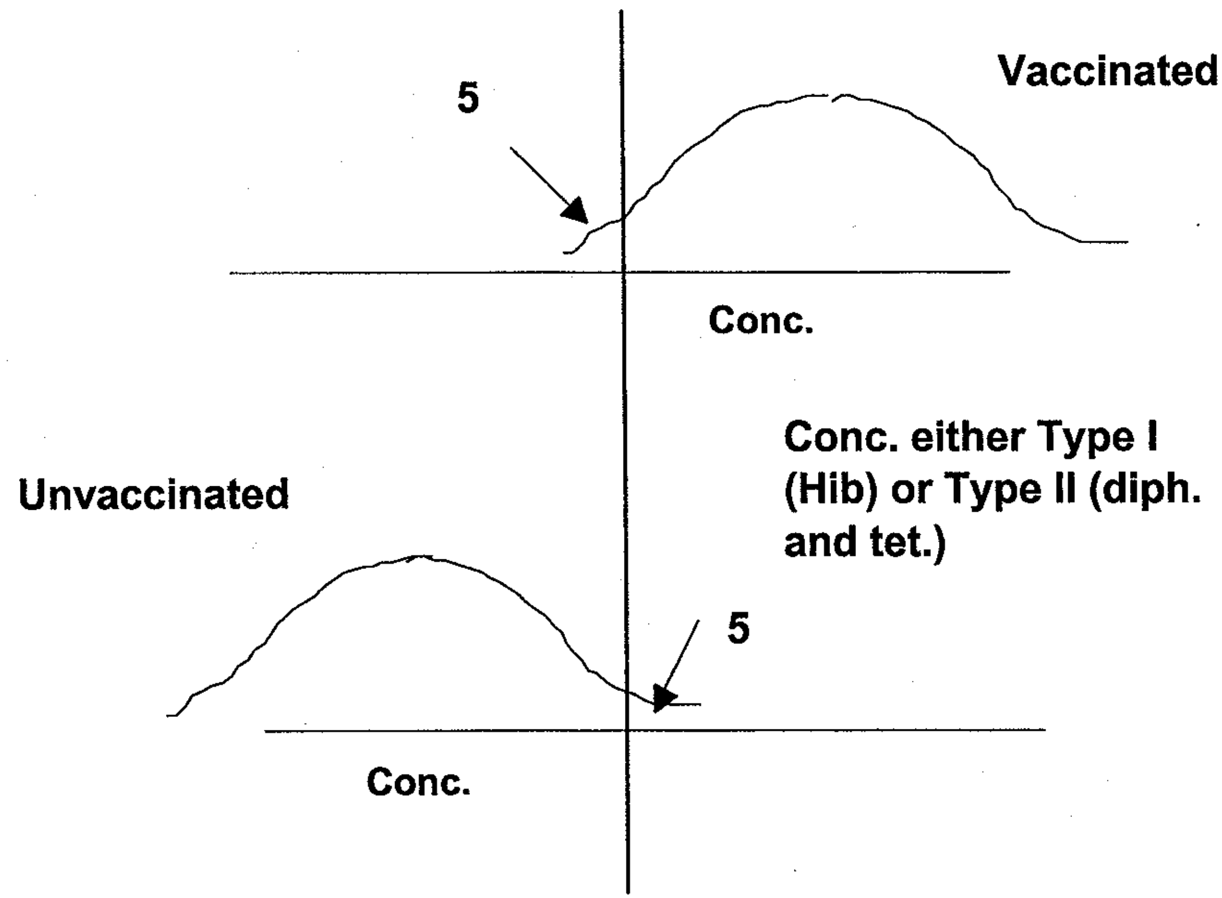
- Population based - H. influenza, diphtheria, tetanus

- Concentration specific

Historical Model
Population Based

- Measure antibody levels in vaccinated and unvaccinated groups
- Protective level is that which is exceeded by most of the vaccinated group and not reached by most of the unvaccinated group
- Problem: arbitrary

Historical Model
Population Based



Conc. either Type I (Hib) or Type II (diph. and tet.)

Concentration Specific Model
Logistic Predictive Model of Disease

Probability of disease given a concentration and exposed =

$$p(D|c,E) = y = e^{a+bc}/\ 1+e^{a+bc}$$

where a,b are constants to be estimated
c = concentration

y = probability between 0.0 and 1.0
a = log odds of disease when t = 0
b = change in log odds of disease with unit change in concentration

Vaccine Efficacy

$$VE = 1 - \frac{\text{disease rate given treated}}{\text{disease rate given not treated}}$$

$P(D|T)$ = prob (disease given treated)
$P(D|NT)$ = prob (disease given not treated)

$$VE = 1 - \frac{P(D|T)}{P(D|NT)}$$

Vaccine Efficacy

$$VE = 1 - \frac{P(D|T,E)P(E|T)}{P(D|NT,E)P(E|NT)}$$

since in a randomized, double-blind trial

$P(E|T)=P(E|NT)$ then

$$VE = 1 - \frac{P(D|T,E)}{P(D|NT,E)}$$

now, let c = concentration

$p(D|c,E) = e^{a+bc} / (1 + e^{a+bc})$ = logistic model

Vaccine Efficacy

$$VE = 1 - \frac{\int p(D|c,E)f(c|T)dc}{\int p(D|c,E)f(c|NT)dc}$$

$$= 1 - \frac{E_T[p(D|c,E)]}{E_{NT}[p(D|c,E)]}$$

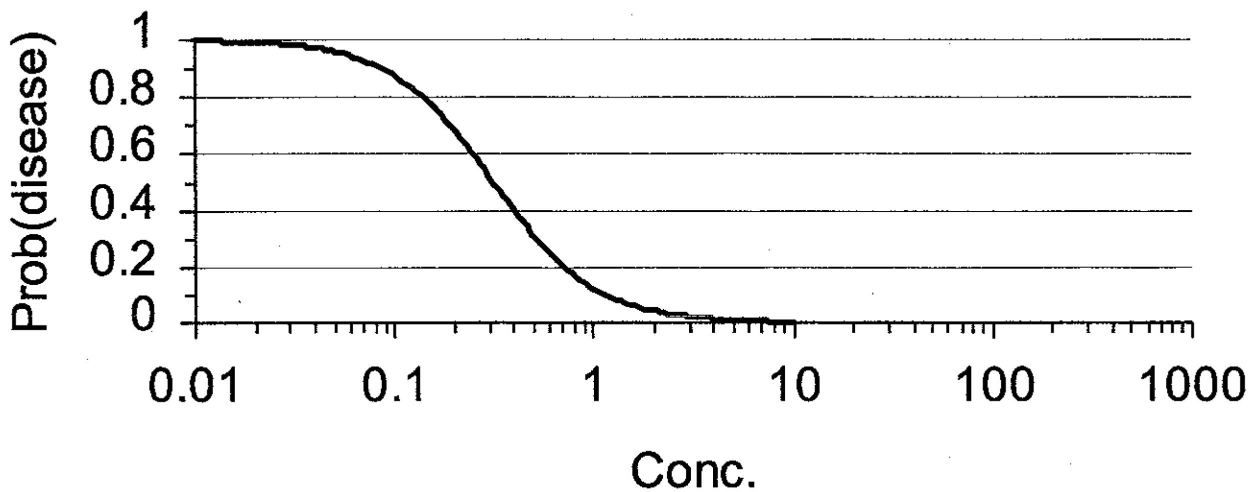
$$VE = 1 - \frac{\text{expected disease rate - treated}}{\text{expected disease rate - not treated}}$$

Vaccine Efficacy Estimate

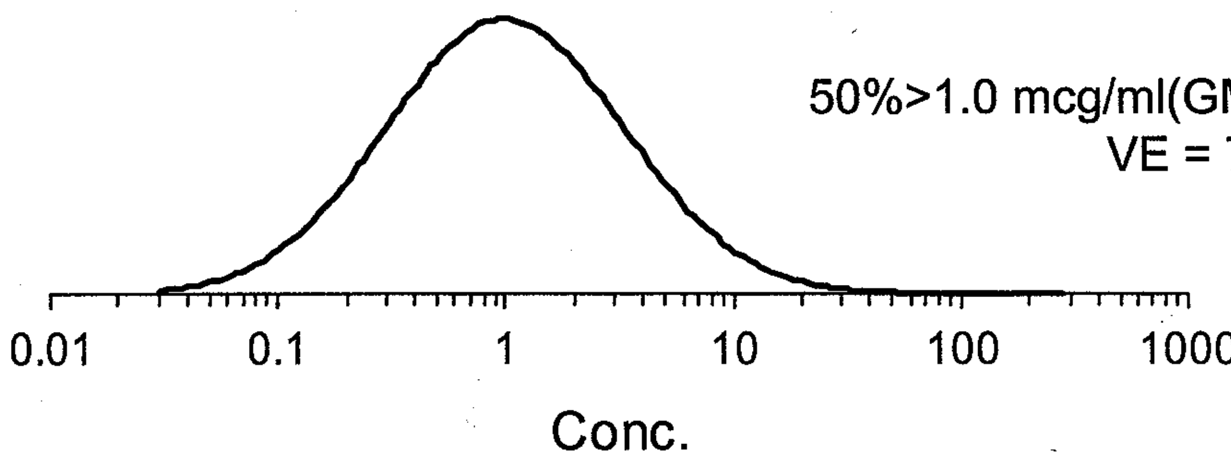
$$VE = \frac{\dfrac{\sum_j \dfrac{e^{a+bc_j}}{1+e^{a+bc_j}}}{n}}{\dfrac{e^a}{1+e^a}}$$

$j = 1, \ldots, n$
n = number of subjects in immunogenicity trial
c_j = conc. in the j-th subject of the trial

Correlates-Immunogenicity Vaccine Efficacy



Logistic model
a=-1.97 b=-1.71



50%>1.0 mcg/ml(GMC=1.0,sd=1.2)
VE = 77%

Theoretical Issues
Concentration Specific Model

- Accounting for the time-varying nature of the disease risk due, possibly, to the time-varying nature of the immunologic measurement

- Accounting for the follow-up time

Extending the Concentration Specific Model
Logit Model

$$\ln(\text{logit}) = a + b^* \ln(\text{conc})$$
$$= a + b^*(c_0 + f^*\text{time})$$

$c_0 = \ln(\text{initial concentration})$

(assuming exponential decay of immunologic measurement)

- for those without disease time is censored
- Cox regression applications ?

Practical Issues

- Limited number of disease cases
- Limited amount of immunology information
- Level of noise in logit estimation is high considering often only 10-15% of population is exposed to disease
- Differing antibody decay characteristics between subjects

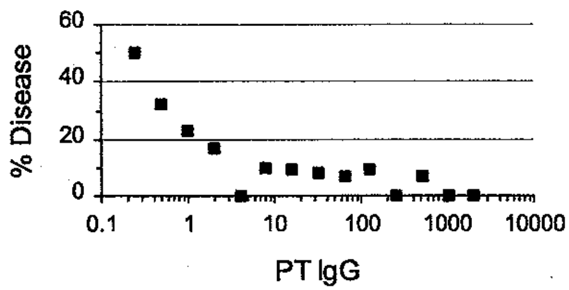
Example: Pertussis Trials

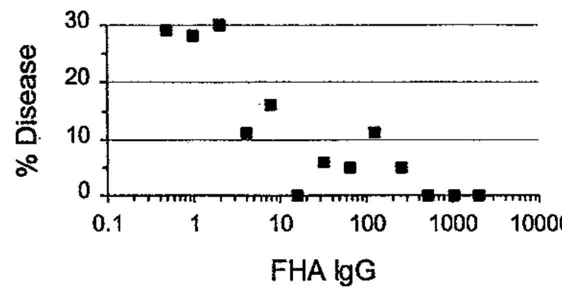
- Cherry, et. al, Vaccine, 1998, 16:1901-1906
  Storsaeter, et. al., Vaccine, 1998, 16:1907-1916
- Use pre-exposure measurement (Type II) - imputed - and simple logistic model
- Do not back estimate to Type I post vaccination measurement

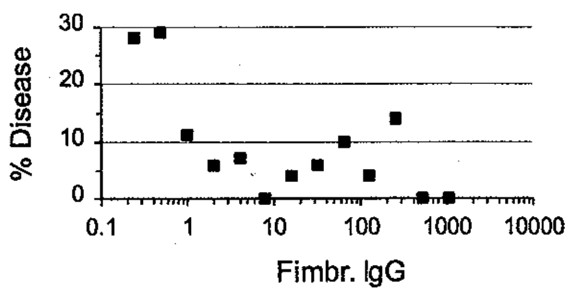
Erlangen Acellular Pertussis Trial

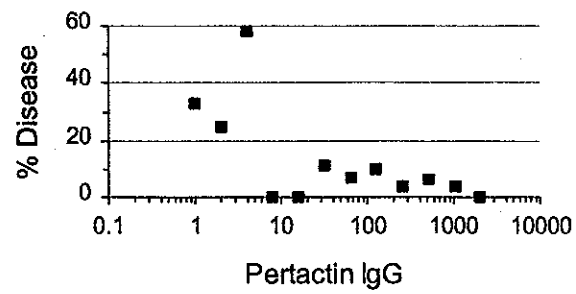
Household Contact Sample (subjects exposed in their household)

% Disease vs. Antibody Conc. after primary series



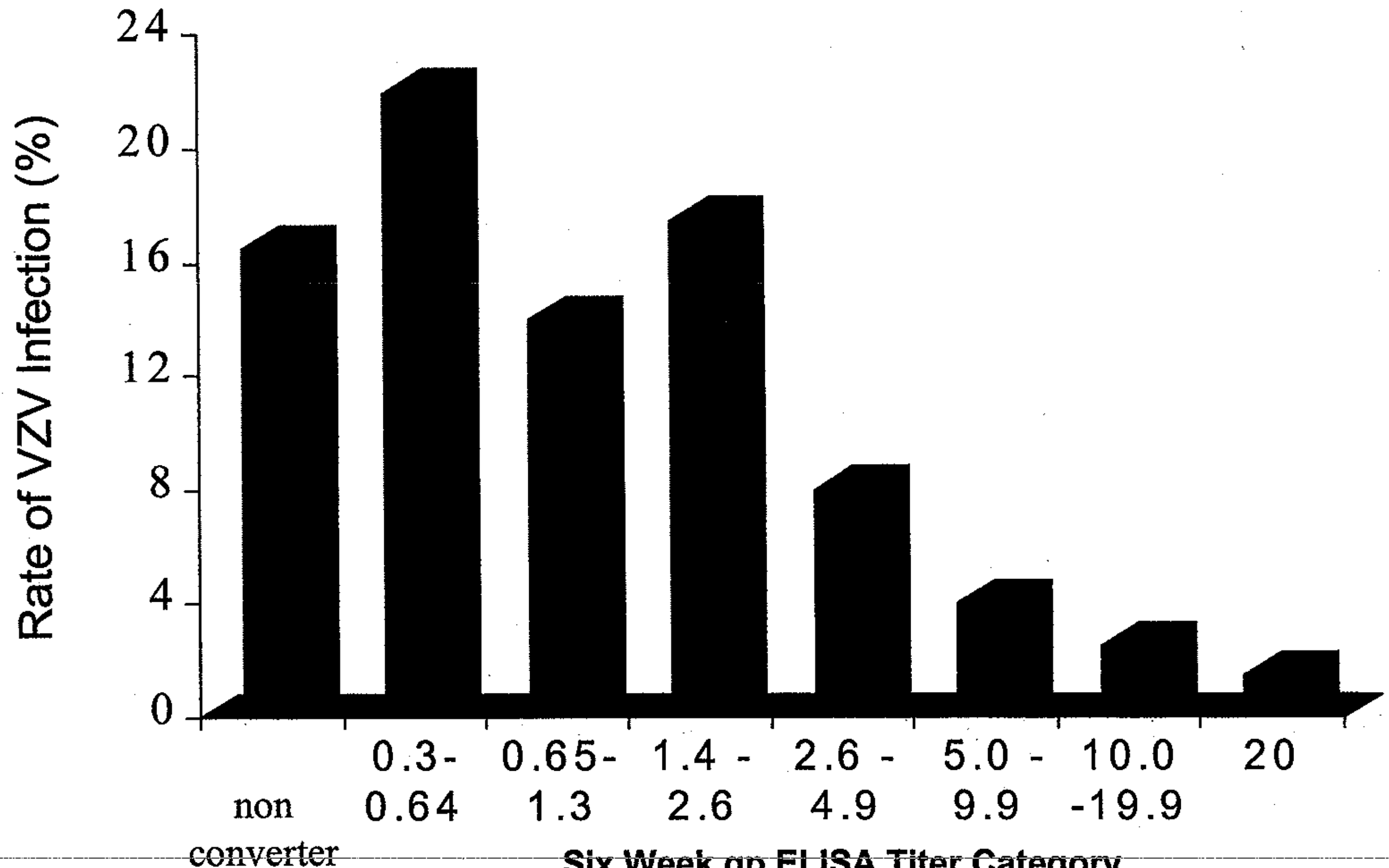






Rate of Varicella* After VZV Vaccine

Adapted from: CJ White et al PIDJ 11:19-23, 1992



Number at Risk	114	55	188	240	370	623	893	996

Two year follow up

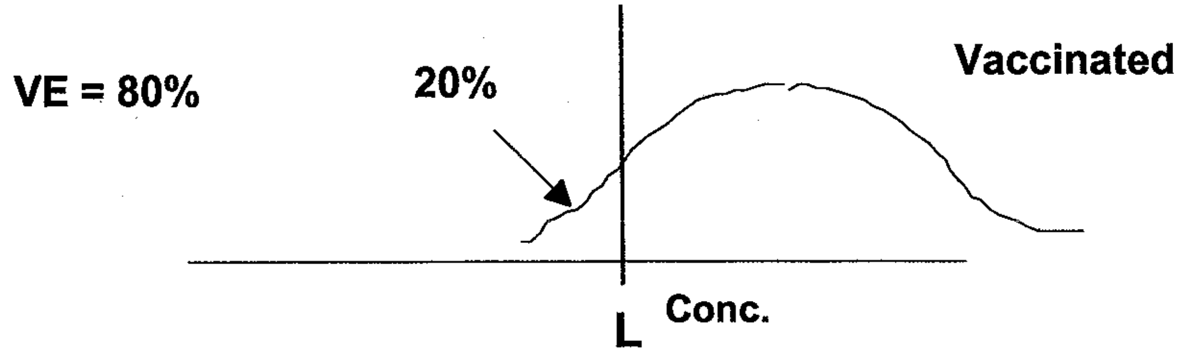
Population Based Model
Is there a Justification?

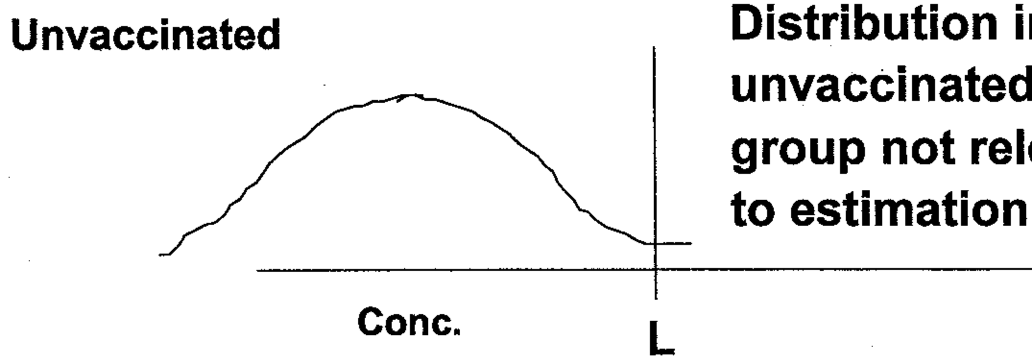
$$\text{Prob (disease)} = \begin{cases} 0 & \text{if measurement} \geq L \\ b & \text{if measurement} < L \end{cases}$$

$$\Downarrow$$

VE = % of population with measurement $\geq$ L

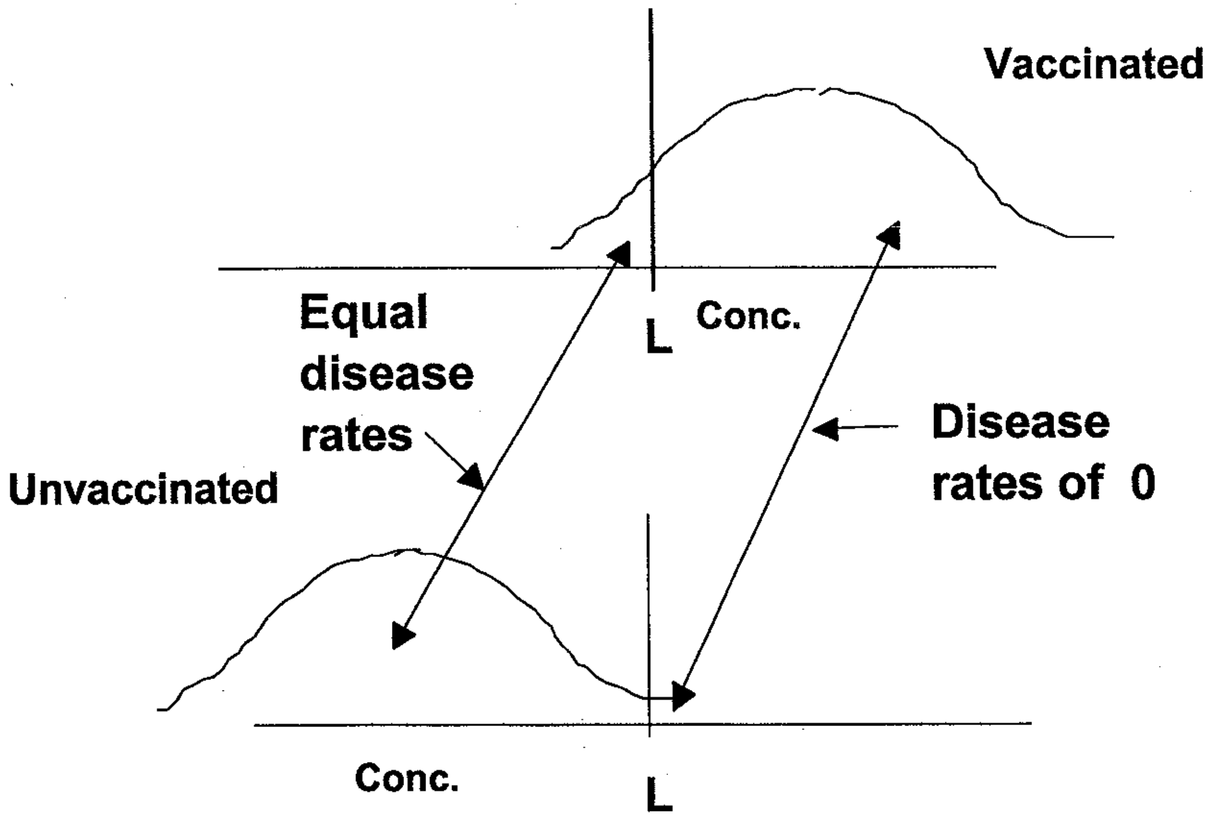
Population Based Model





Distribution in unvaccinated group not relevent to estimation

Population Based Model
Model Check



Basic Immunology Issues Serology IgG Measurements

- Relationship of assay measurement with opsonic or virus neutralizing capability (functional antibody)
- Amount and speed of anamnestic response
- Mucosal and cellular immunity

Conclusions

- Concentration specific models may be too impractical for common use

- Population based models may provide a sufficient approximation